Poly(dimethylsiloxane) Coatings for Controlled Drug Release. II. Mechanism of the Crosslinking Reaction in Emulsion

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ABSTRACT: Earlier work focused on the crosslinking of hydroxyl-terminated poly(dimethylsiloxane) (PDMS) particles in a stable latex suitable for spraying onto drug tablets, and established the conditions for eliminating the usual toxic catalysts that would be unacceptable in such pharmaceutical coating materials. Use of these coatings for controlling the rate of release of a drug, however, requires a better understanding of their properties and thus clarification of the mechanism through which the crosslinking occurs. The present study approaches this goal by documenting the effects of anionic, cationic, and nonionic surfactants at various concentrations, and in acidic, neutral, or basic media. FTIR spectroscopy was used to monitor the transportation of crosslinker from the water phase into the hydrophobic PDMS phase. The results suggest a possible mechanism for the crosslinking in sufficient detail to be used to optimize the coatings for drug-release applications. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 91: 2186–2194, 2004

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INTRODUCTION

Hydroxyl-terminated chains of poly(dimethylsiloxane) (PDMS) [$-Si(CH_3)_2O-$] have been extensively used to form elastomeric networks by end-linking them with tetraethoxysilane (TEOS) [$Si(OC_2H_5)_4$], using organic tin or platinum catalysts. One such application is the preparation of "model" networks for evaluating the molecular theories of rubberlike elasticity.[1–3] Recently, such polysiloxane or "silicone" elastomers were also evaluated as pharmaceutical coating materials,[4–10] and there have been a number of relevant reports related to the preparation of both the PDMS elastomers and their dispersions in latices.[11–14] Only now, however, has this work been concerned with the PDMS crosslinking reaction in emulsions without the usual organic tin catalysts. Because such catalysts are toxic, they would have to be eliminated in products for pharmaceutical uses.

Our previous studies were successful in identifying conditions for preparing stable PDMS latices without any organic tin catalyst. The latices were found to be suitable in a spray-coating process giving smooth relatively robust coatings on drug tablet cores.[15,16] The unmodified coating was found to protect these cores very well even in acidic or basic media. *In vitro* evaluations showed no drug release in acidic or basic media for at least 24 h. Increasing the release to a desired level was accomplished by using a channeling agent such poly(ethylene glycol) (PEG; molecular weight 8000 g/mol) to produce tunnels through the PDMS. However, the results were not entirely satisfactory. The addition of 50% (w/w of PDMS) of PEG to a PDMS film gave only 50 to 60% zero-order release over 24 h, and 100% non-zero-order release in approximately 3 days.[16] To produce a coating giving the desired rate of 100% zero-order release in 1 day would require modifications in the PDMS films themselves. Ultimately, this will probably require making the chains less hydrophobic and controllable tunnel structure, but better control of the degree of crosslinking should also be helpful. Such control requires a better molecular understanding of the crosslinking mechanism, and achieving this was the purpose of the present investigation.

In this study, the crosslinking reaction between PDMS and crosslinker in emulsion was extensively investigated. Of particular importance was preparing the emulsion using various kinds of surfactants at several concentrations, investigating the effects of the pH of the reaction medium, and the use of two crosslinkers, specifically TEOS and triethoxy(vinyl)silane (TEVS). The vinyl groups in the TEVS served as markers that could be monitored by Fourier transform

infrared (FTIR) spectroscopy to characterize transport of the crosslinking agent into the PDMS phase. The goal was a mechanism for the crosslinking that was sufficiently detailed to be used to optimize the coatings for pharmaceutical applications.

EXPERIMENTAL

Materials

A sample of hydroxyl-terminated PDMS (designated Q1-3563; number-average molecular weight 3×10^3 g/mol) and Dow Corning 193 surfactant (polyoxyethylene methylpolysiloxane copolymer, DC193) were kindly provided by the Dow Corning Corp. (Midland, MI). Sodium lauryl sulfate (SLS) was obtained from Fisher Scientific (Pittsburgh, PA). Dioctyl sulfosuccinate sodium salt (DOS), 1-hexadecanesulfonic acid sodium salt (HS), dodecylbenzenesulfonic acid sodium salt (DBS), cetyltrimethylammonium bromide (CTAB), Tween 80 (T80), TEOS, TEVS, and solvents such as toluene, acetone, and methanol were obtained from Aldrich (Milwaukee, WI). All of these materials were used as received. Concentrated hydrochloric acid and ammonium hydroxide (both from Aldrich) were diluted to $1M$ before use.

Preparation of the PDMS emulsions

Emulsions of 30% PDMS in water were prepared by ultrasonic processor (Vibra Cell High Intensity Ultrasonic Processor Model VC 600; Sonics Materials Inc., Danbury, CT) for 20 min at room temperature with 1% surfactant.[15] The PDMS particles in the emulsion had diameters around 0.4 μm, and the viscosity of the emulsion was about 5.0 cp. To facilitate comparisons with the different surfactants and crosslinkers, the same formulations and reaction conditions were used.

Monitoring the crosslinking reaction by gel content measurements

Emulsion samples (about 0.5 g) were collected after various crosslinking reaction times (0, 1, 2, 3, 4, 6, 10, and 24 h) and then weighed. The emulsions were broken using a 1 : 1 acetone–methanol mixture, and the oil or solid-gel phase was carefully separated from the solvent phase. Toluene was added to the oil or solid-gel phase and mixed and shaken for 2 min to dissolve the uncrosslinked portions. The solid-gel phase was separated from the toluene and dried under vacuum at room temperature for 24 h before being weighed. Gel contents, suitable for describing the extent of the crosslinking, were calculated from the weights obtained.

Monitoring the crosslinking reaction by FTIR spectroscopy

TEVS was used as crosslinker in this study instead of TEOS, with other aspects of the crosslinking remaining the same. A small amount of emulsion sample (~ 0.5 g) was collected at various crosslinking reaction times. After the emulsions were broken, the oil or solid-gel phase was carefully separated from the solvent phase and placed between CaF_2 windows. They were examined by FTIR (Perkin–Elmer Spectrum One; Perkin Elmer Cetus Instruments, Norwalk, CT) over 4500 to 1000 cm^{-1}, with 4 cm^{-1} resolution.

TEVS entering the PDMS droplets would be identified through its vinyl groups, as monitored by the FTIR measurements. To do this quantitatively, a reference peak remaining very nearly constant during the reaction must be used. In this system, the concentration of Si—CH_3 groups served this purpose. Thus, the ratio of the peak area for the vinyl group relative to that of the Si—CH_3 group can be used to describe the extent of crosslinking. The peak chosen for the vinyl group was around 1603 cm^{-1} and that for the Si—CH_3 group around 1259 cm^{-1}. Values of the ratio of two areas were plotted as a function of reaction time.

RESULTS AND DISCUSSION

PDMS crosslinking reaction in emulsion with anionic surfactants

Effects of pH

The pH effects on crosslinking reaction of emulsion were studied in acid (pH 2, adjusted by using $1M$ HCl), base (pH 10, adjusted by using $1M$ NH$_4$OH), and neutral condition (in distilled water).

The solid (gel) contents obtained as a function of reaction time are shown in Figure 1. During the first day no solid gel was produced when reactions were carried out in neutral or basic conditions in the absence of organic tin catalyst, and this lack of gelation persisted for at least 100 h. As expected, crosslinking did occur within 40 h under basic conditions if an organic tin catalyst was used.[17,18] This demonstrates that the reaction between PDMS and TEOS could be effectively carried out in neutral or basic conditions only with the use of a catalyst. On the other hand, under acidic conditions gelation occurred without a organic tin catalyst within 30 min, and the reaction proceeded to greater than 90% gel within 3 h.

Previous thermogravimetric analysis (TGA) results indicated that the decomposition temperature increased about 150°C after the crosslinking reaction.[15] Additionally, the materials obtained were sufficiently robust for mechanical property measurements carried out in the usual manner.

Effects of SLS content

Figure 2 shows the effects of varying amounts of SLS on the crosslinking reaction. The reaction with 0.25% (w/w) SLS showed relatively long gel times and low solid con-
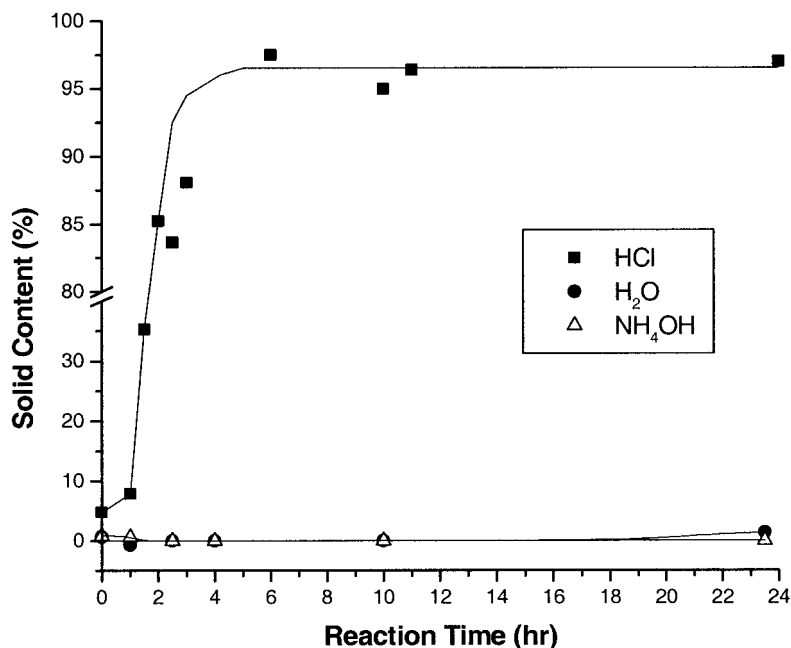
Figure 1 Rates of generation of gel from crosslinking poly(dimethylsiloxane) (PDMS) in emulsions with sodium lauryl sulfate (SLS) surfactant, for acidic, neutral, and basic media.

tents. Because this SLS concentration was in the vicinity of the critical micelle concentration of the SLS,[19–21] this amount of surfactant was probably not sufficient to stabilize the PDMS particles in the emulsion or latex very well. In fact, the emulsion was unstable, and some large, apparently agglomerated, particles appeared during the reaction. The crosslinking reaction rate increased when the amount of SLS increased from 0.25 to 1.0%. This was probably attributable to the increased amount of SLS at the interface facilitating transport of the crosslinker into the hydrophobic PDMS droplets. However, when the amount of SLS was increased to 1.5%, the gel time increased from about 2.5 to 3.0 h. This was probably a result of the higher concentrations of SLS producing thicker protective layers around the PDMS droplets, suppressing the inward transport of the crosslinker.
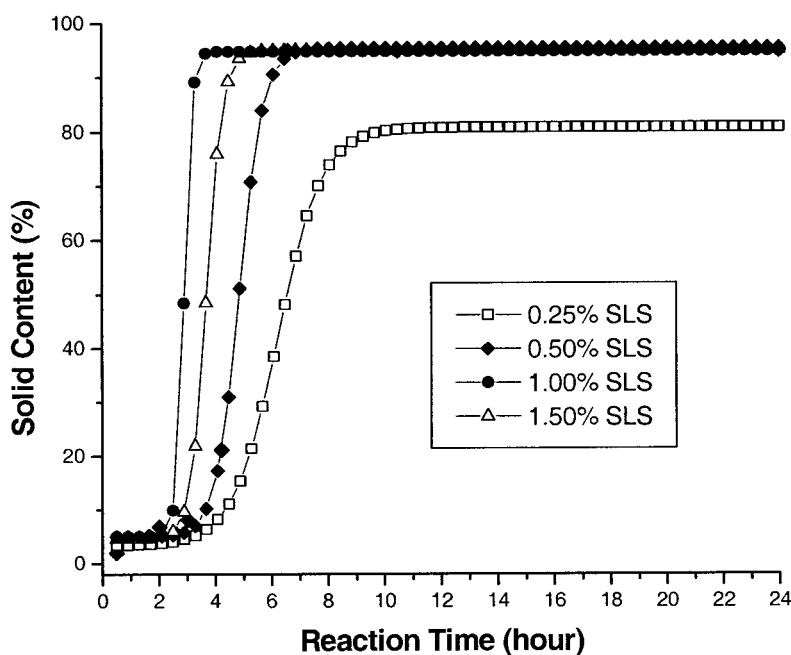

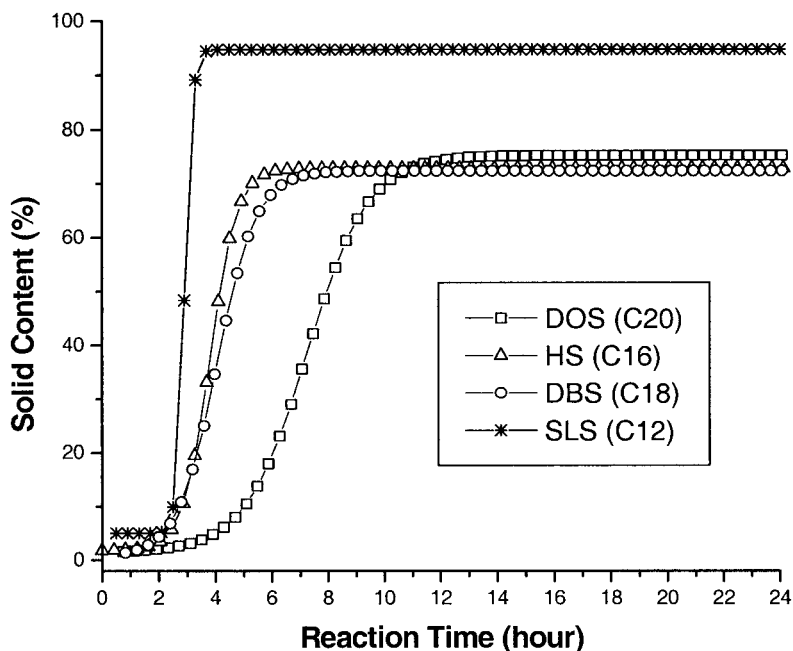**Figure 2** Effects of SLS content on the crosslinking reaction.

Figure 3 Effects of anionic surfactant content on the crosslinking reaction.

Effects of various anionic surfactants

The results using some sulfonic types of anionic surfactants having various carbon chain lengths are shown in Figure 3. The concentration for each surfactant was maintained at 1% (w/w), no organic tin catalyst was present, and the reactions were carried out under acidic conditions. As before, the absence of catalyst prevented gelation in the case of neutral or basic conditions. This type of sulfonic surfactant thus behaved very similarly to the SLS sulfate surfactant. The main difference between the sulfate and sulfonic surfactants was the percentage conversion to gel. For SLS, it was possible to obtain 90–100% gel, although the sulfonic type yielded at most about 70% gel. This was probably attributable to the different structures of the two kinds of surfactants. Perhaps the additional oxygen atom between the carbon chain and the sulfur atom in SLS facilitates transport of the crosslinker into the PDMS.

It was noted that the longer the carbon chains in the sulfonic surfactants, the slower the crosslinking reaction. The crosslinking reaction for DOS (20 carbons in the hydrophobic tail) required 3 to 4 h longer than for HS (16 carbons). The longer hydrophobic tail apparently made transport of the crosslinker from the water phase to the PDMS phase more difficult.

Effects of other types of surfactants

The results on the other kinds of surfactants, nonionic (T80) and cationic (CTAB) surfactants, are shown in Figure 4. In the absence of catalyst, no PDMS gel appeared with either T80 or CTAB, under acidic, neu-

tral, or basic conditions. This suggested that the T80 and CTAB surfactants were not able to transport TEOS to the PDMS droplets to facilitate the reaction.

To test this conclusion, some SLS was added to the emulsions with T80 as surfactant to see whether it could function as "catalyst" under these conditions. The results, included in Figure 4, supported this idea, although the reaction rate was much slower than that when the SLS was present as a surfactant. This decrease in effectiveness was probably attributable to the nonionic T80 forming a protective layer hindering the desired transport of TEOS into the PDMS droplets. Furthermore, the increase in the amount of SLS from 0.5 to 1% (w/w) decreased the gel time from about 20 to 10 h. This clearly indicated that SLS could activate the reaction.

FTIR results on the crosslinking reaction

The goal here was to detect either the functional groups of the crosslinker or new functional groups formed during the crosslinking reaction. The presence of water in the system made it impossible to clearly detect the hydroxyl groups used in the reaction, and the newly formed Si—O—Si groups could not be distinguished, given that a large number of such bonds were already present in the PDMS. The focus was therefore on the vinyl groups present as markers in the TEVS [CH_2=$CHSi(OC_2H_5)_3$], which was used in exchange for TEOS [$Si(OC_2H_5)_4$] in these studies. The vinyl group has a very clear absorption peak in the IR spectrum at around 1602 cm^{-1}, attributed to the car-
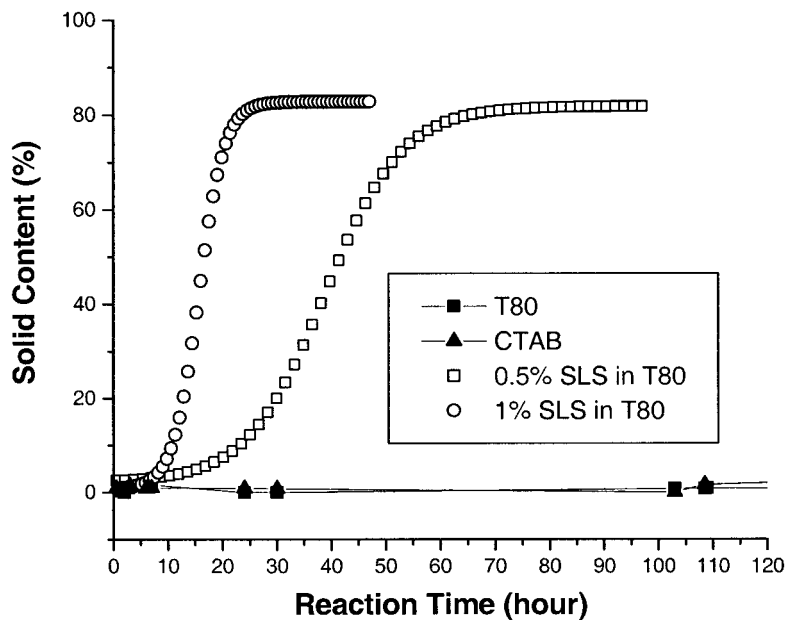
Figure 4 Effects of various surfactant formulations on the crosslinking reaction.

bon–carbon double-bond stretching.[22] This was the peak used to monitor the TEVS crosslinker entering the PDMS phase for the crosslinking process.

Figure 5 shows the examples of IR spectrum of the TEVS, and for the reactants after 0 h and the 24-h reaction. The TEVS showed the strong absorption peak at 1602 cm^{-1}, but the reactants did not at 0 h and did show that peak during the reaction and at 24 h. The peak around 1259 cm^{-1}, attributed to the Si—CH$_3$ symmetric CH$_3$ deformation modes,[23] occurred for the reactants even at 0 h. It was thus useful as a constant, reference peak.
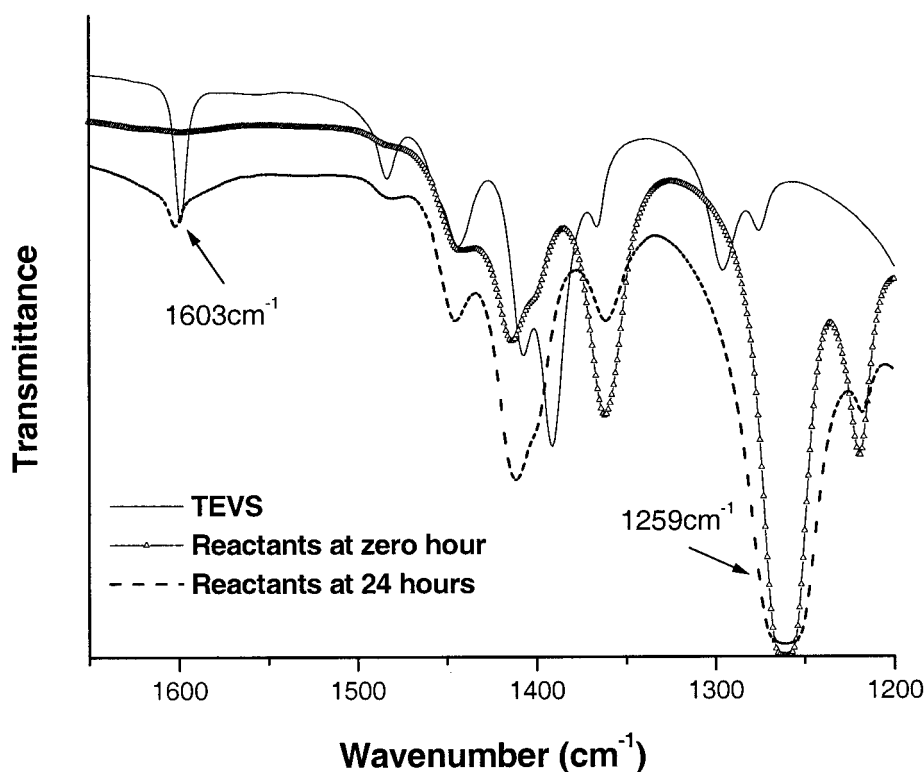

Figure 5 Time dependency of the FTIR spectra for tetraethoxy(vinyl)silane in PDMS reactants.
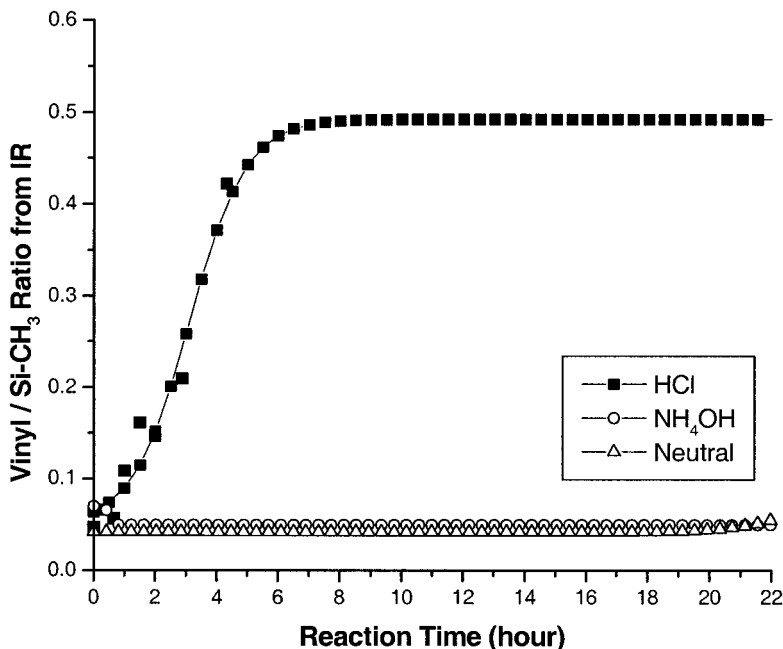
Figure 6 FTIR determinations of vinyl contents as function of reaction time for SLS surfactant, in acidic, basic, and neutral media.

The IR results for the crosslinking reaction in acidic, neutral, and basic conditions are presented in Figure 6. Again, the crosslinking reaction without organic tin catalyst is seen to occur only in the acidic medium, confirming that the crosslinkers could not enter the PDMS phase under basic or neutral conditions. All of these results closely parallel those from the gel measurements, summarized in Figure 1.

The two approaches were further compared by taking two samples after the same time intervals during the crosslinking reaction, one for the IR test and the other for gel content determination. The results, shown in Figure 7, show the close parallel over most of the time interval. The only minor difference appeared at the beginning of the reaction, when the gel contents were very small in spite of the fact that a
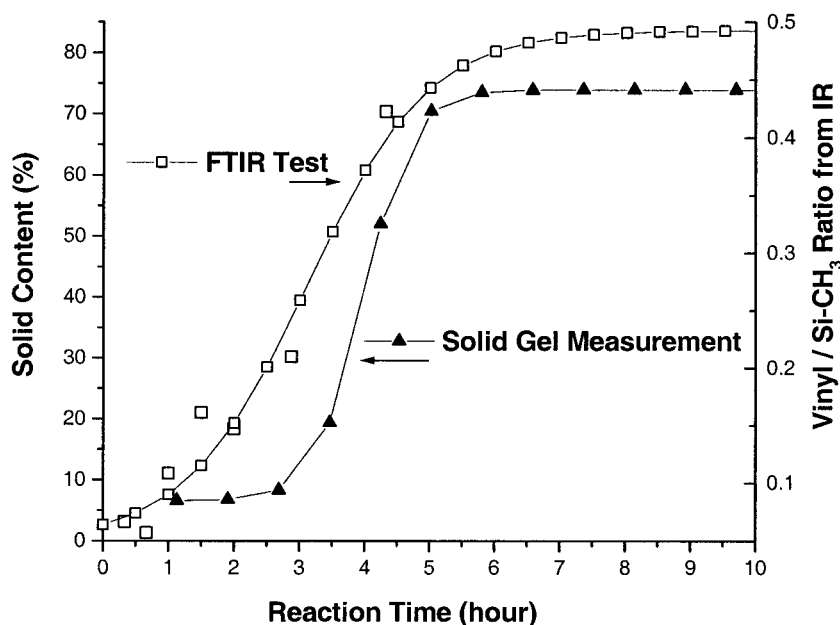

Figure 7 Comparisons of FTIR spectral results and solid gel contents for determining the extents of reaction, with SLS surfactant in acidic medium.
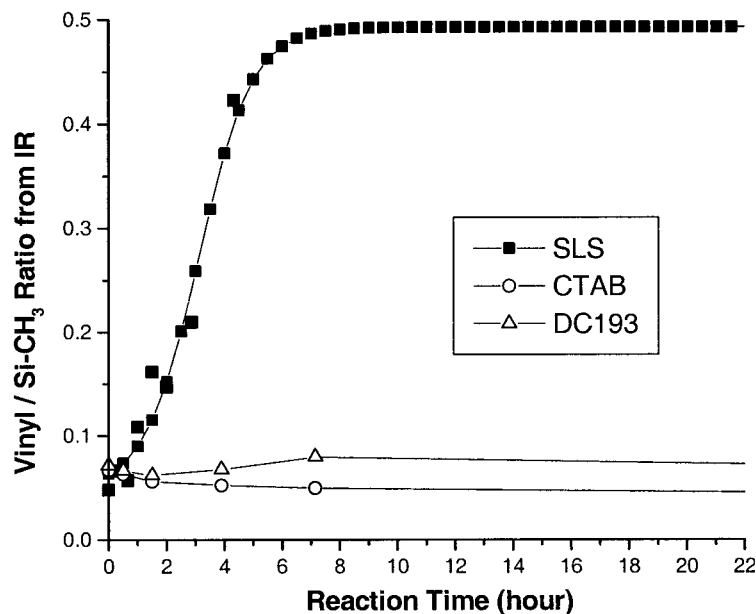
Figure 8 FTIR results for extents of reaction, for the specified surfactants in acidic media.

significant amount of crosslinkers had already entered the PDMS phase. The crosslinking was presumably proceeding at this early stage but not to the point of forming a gel, or the gel that had formed was very fragile.

A final series of FTIR measurements was carried out on emulsions having different surfactants. Because T80 also contains carbon–carbon double bonds, it was not suitable for IR testing. Dow Corning 193 nonionic surfactant was used instead. Figure 8 shows the results, which were almost the same as those from the gel content measurements, and were thus consistent with all the preceding results and conclusions.

Mechanism of the crosslinking reaction in emulsion

According to previous reports,[17,18,24] the crosslinking reaction between hydroxyl-terminated PDMS and TEOS in emulsion usually involves two steps. The first is hydrolysis of TEOS under acid or base catalysis. In the second, the hydrolysis products are transported into the oily PDMS phase followed by polycondensation between the terminal silanol groups of the PDMS and the OH groups of the partially hydrolyzed TEOS. It is this second step that would be facilitated by an organic tin catalyst.

In emulsions, if the hydrolyzed crosslinkers are not transported into the oily PDMS phase, there is little chance for a reaction between PDMS and the crosslinkers. Moreover, the surfactants would also prevent hydrolyzed crosslinkers from being transferred from the water phase to the PDMS oil phase, if there was no catalyst to facilitate this transport.

As was demonstrated by gel content measurement and FITR characterization, the TEOS and TEVS crosslinkers could not be transported to the PDMS surface or into the hydrophobic PDMS droplets even under acidic conditions if cationic or nonionic surfactants were used. However, an addition of SLS could help such transportation in the nonionic or cationic cases, although the reactions were quite slow. The results suggested that the SLS surfactant in the interfaces between PDMS and water could help transport hydrolyzed crosslinkers to the surfaces of the PDMS oil droplets under acidic conditions. These conclusions, together with other evidence,[15] suggest the possible mechanism outlined in Figure 9.

Under acidic conditions, the TEOS first hydrolyzes to form silicic acid or water-soluble silicates. The hydrolyzed TEOS could then combine with the acidified anionic surfactant, such as sodium lauryl sulfate, and be transported to the surfaces of the hydrophobic PDMS droplets. This transport of the crosslinker is a critical step for the crosslinking reaction.

The actual crosslinking reaction would then occur between the hydroxyl end groups of PDMS and the hydroxyl groups in the hydrolyzed TEOS. Because of the highly hydrophobic nature of PDMS, the water from the crosslinking reaction would be removed from the oily droplets to the water phase. This is probably the driving force that permits the crosslinking reaction to go to completion.

CONCLUSIONS

The crosslinking reaction between hydroxyl-terminated poly(dimethylsiloxane) and tetraethoxysilane in
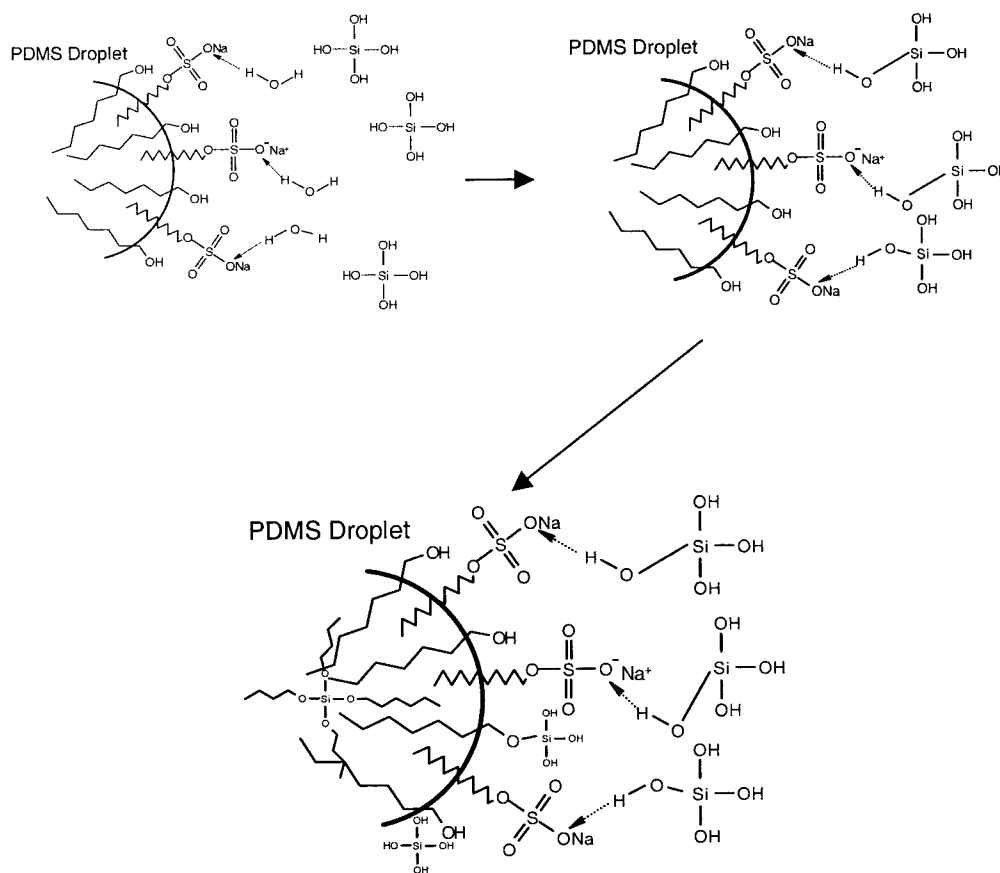
Step 1.
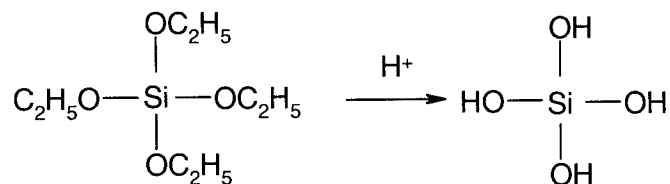
Step 2.

Figure 9 Possible mechanism for the PDMS crosslinking reaction in emulsion.

emulsions could be carried out without the usual organic tin catalysts only in the case of acidic media. Anionic surfactant agents, such as sodium lauryl sulfate, served not only as a surface-active agent, but also as a facilitator for the crosslinking. This reaction did not occur in the cases of the cationic and nonionic surfactants. Gel contents and FTIR spectra characterized the crosslinking reaction and gave analogous results. Based on these results, a crosslinking reaction mechanism could be posited. The understanding of the fundamental mechanisms of the crosslinking reaction should provide valuable guidance in the modification of PDMS coatings for use in a variety of applications, including formulation of latex coatings for controlling release rates in drug-delivery systems.

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